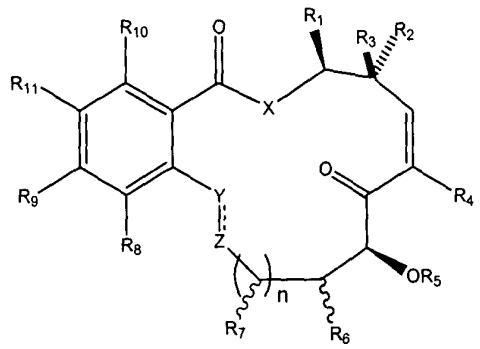
CLAIMS

We claim:

1. A pharmaceutical composition for systemic administration comprising a compound having the structure:



(I)

or pharmaceutically acceptable derivative thereof;

wherein $\mathbf{R_1}$ is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl;

$\mathbf{R_2}$ and $\mathbf{R_3}$ are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or

R_1 and R_2, when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms; or

R_1 and R_3, when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms;

$\mathbf{R_4}$ is hydrogen or halogen;

$\mathbf{R_5}$ is hydrogen, an oxygen protecting group or a prodrug;

$\mathbf{R_6}$ is hydrogen, hydroxyl, or protected hydroxyl;

n is 0-2;

$\mathbf{R_7}$, for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

$\mathbf{R_8}$ is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or an aliphatic moiety optionally substituted with hydroxyl, protected hydroxyl, SR_{12}, or $NR_{12}R_{13}$;

R_9 is hydrogen, halogen, hydroxyl, protected hydroxyl, OR_{12}, SR_{12}, $NR_{12}R_{13}$, $-X_1(CH_2)_pX_2-R_{14}$, or is lower alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or $-X_1(CH_2)_pX_2-R_{14}$;

wherein R_{12} and R_{13} are, independently for each occurrence, hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or a protecting group, or R_{12} and R_{13}, taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of R_{12} and R_{13} are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein X_1 and X_2 are each independently absent, or are oxygen, NH, or -N(alkyl), or wherein X_2-R_{14} together are N_3 or are a saturated or unsaturated heterocyclic moiety,

p is 2-10, and

R_{14} is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is $-(C=O)NHR_{15}$ $-(C=O)OR_{15}$, or $-(C=O)R_{15}$, wherein each occurrence of R_{15} is independently hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or R_{14} is $-SO_2(R_{16})$, wherein R_{16} is an aliphatic moiety, wherein one or more of R_{14}, R_{15}, or R_{16} are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

R_8 and R_9 may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

R_{10} is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

R_{11} is hydrogen, hydroxyl or protected hydroxyl;

X is absent or is O, NH, N-alkyl, CH_2 or S;

Y is CHR_{17}, O, C=O, CR_{17} or NR_{17}; and **Z** is CHR_{18}, O, C=O, CR_{18} or NR_{18}, wherein each occurrence of R_{17} and R_{18} is independently hydrogen or aliphatic, or R_{17} and R_{18} taken

together is –O-, -CH_2- or -NR_{19}-, wherein R_{19} is hydrogen or lower alkyl, and Y and Z may be connected by a single or double bond; and

a pharmaceutically suitable carrier or diluent.

2. The composition of claim 1, wherein:

R_1 is hydrogen, straight or branched lower alkyl, straight or branched lower heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl;

R_2 and **R_3** are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, straight or branched lower alkyl, straight or branched lower heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl; or

R_1 and R_2, when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen; or

R_1 and R_3, when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen;

R_4 is hydrogen or halogen;

R_5 is hydrogen or a protecting group;

R_6 is hydrogen, hydroxyl, or protected hydroxyl;

n is 0-2;

R_7, for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

R_8 is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or lower alkyl optionally substituted with hydroxyl, protected hydroxyl, SR_{12}, or $NR_{12}R_{13}$;

R_9 is hydrogen, halogen, hydroxyl, protected hydroxyl, OR_{12}, SR_{12}, $NR_{12}R_{13}$, -$X_1(CH_2)_pX_2$-R_{14}, or is lower alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or -$X_1(CH_2)_pX_2$-R_{14};

wherein R_{12} and R_{13} are, independently for each occurrence, hydrogen, lower alkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or a protecting group, or R_{12} and R_{13}, taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon

atoms and 1 to 3 nitrogen or oxygen atoms, and each of R_{12} and R_{13} are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein X_1 and X_2 are each independently absent, or are oxygen, NH, or -N(alkyl), or wherein X_2-R_{14} together are N_3 or are a saturated or unsaturated heterocyclic moiety,

p is 2-10, and

R_{14} is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is –(C=O)NHR_{15} –(C=O)OR_{15}, or –(C=O)R_{15}, wherein each occurrence of R_{15} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or R_{14} is $–SO_2(R_{16})$, wherein R_{16} is an alkyl moiety, wherein one or more of R_{14}, R_{15}, or R_{16} are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

R_8 and R_9 may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

$\mathbf{R_{10}}$ is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

$\mathbf{R_{11}}$ is hydrogen, hydroxyl or protected hydroxyl;

X is absent or is O, NH, N-alkyl, CH_2 or S;

Y is CHR_{17}, O, C=O, CR_{17} or NR_{17}; and **Z** is CHR_{18}, O, C=O, CR_{18} or NR_{18}, wherein each occurrence of R_{17} and R_{18} is independently hydrogen or lower alkyl, or R_{17} and R_{18} taken together is –O-, $-CH_2-$ or $-NR_{19}-$, wherein R_{19} is hydrogen or lower alkyl, and Y and Z may be connected by a single or double bond.

3. The composition of claim 2, where X is oxygen and n is 1.

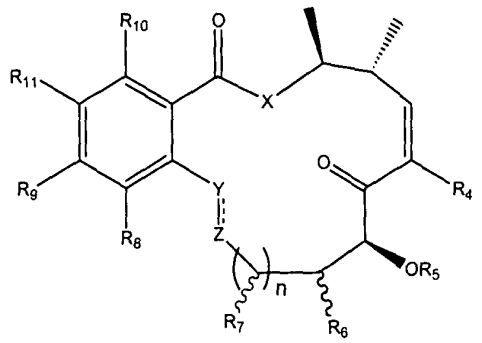
4. The composition of claim 2, where R_4 is halogen.

5. The composition of claim 2, where R_4 is fluorine.

6. The composition of claim 2, where Y and Z together represent-CH=CH-

7. The composition of claim 2, where Y and Z together represent trans –CH=CH-.

8. The composition of claim 2, wherein R_1 and R_2 are each methyl and R_3 is hydrogen and the compound has the structure:



wherein R_4-R_{11}, n, X, Y and Z are as defined in claim 2.

9. The composition of claim 8, wherein X is oxygen and n is 1.

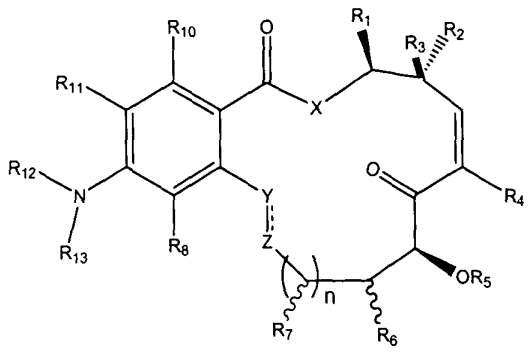
10. The composition of claim 8, wherein R_4 is halogen.

11. The composition of claim 8, wherein Y and Z together represent –CH=CH.

12. The composition of claim 8, wherein X is oxygen, n is 1, R_4 is halogen and Y and Z together represent –CH=CH-.

13. The composition of claim 11 or 12 wherein –CH=CH- is *trans*.

14. The composition of claim 2, wherein R_9 is $NR_{12}R_{13}$ and the compound has the structure:



wherein R_1-R_{12}, n, X, Y and Z are as defined in claim 2, or

R_{13} and R_8 may, when taken together, form a cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydrogen, alkyloxy, amino, alkylamino, aminoalkyl, and halogen.

15. The composition of claim 14, wherein X is oxygen and n is 1.

16. The composition of claim 14, wherein R_4 is halogen.

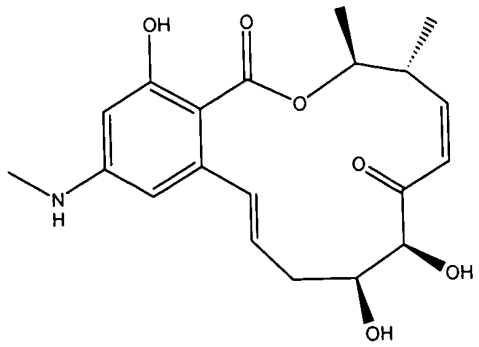
17. The composition of claim 14, wherein Y and Z together represent –CH=CH-.

18. The composition of claim 14, wherein R_1 and R_2 are each methyl and R_3 is hydrogen.

19. The composition of claim 14, wherein X is oxygen, n is 1, R_1 and R_2 are each methyl, R_3 is hydrogen, R_4 is halogen, and Y and Z together represent –CH=CH-.

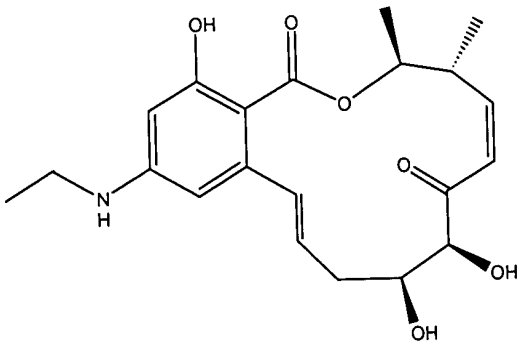
20. The composition of claim 17 or 19, wherein –CH=CH- is trans.

21. The composition of claim 1 wherein the compound has the structure:



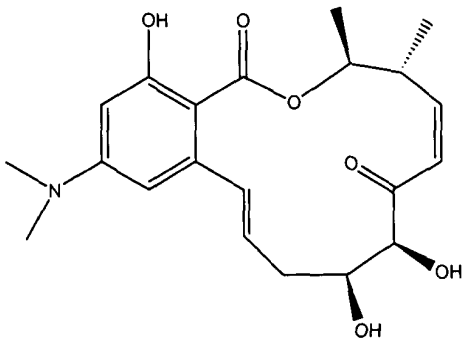
or pharmaceutically acceptable derivative thereof.

22. The composition of claim 1 wherein the compound has the structure:



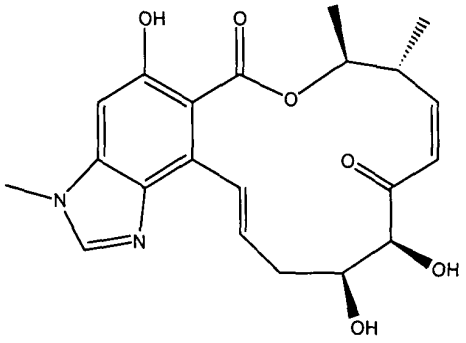
or pharmaceutically acceptable derivative thereof.

23. The composition of claim 1 wherein the compound has the structure:



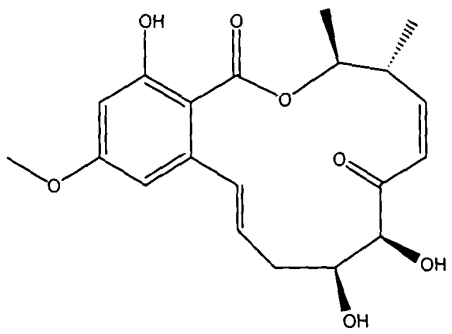
or pharmaceutically acceptable derivative thereof.

24. The composition of claim 1 wherein the compound has the structure:



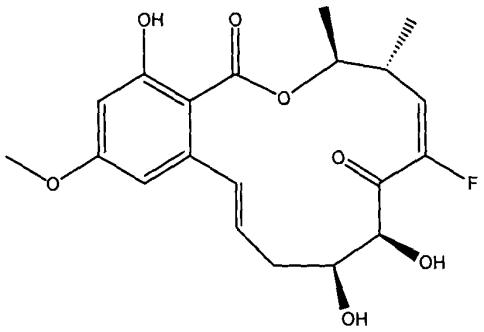
or pharmaceutically acceptable derivative thereof.

25. The composition of claim 1 wherein the compound has the structure:



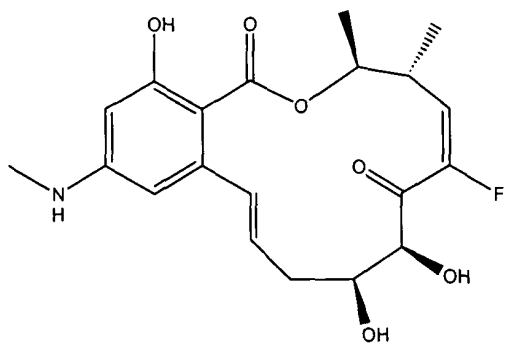
or pharmaceutically acceptable derivative thereof.

26. The composition of claim 1 wherein the compound has the structure:



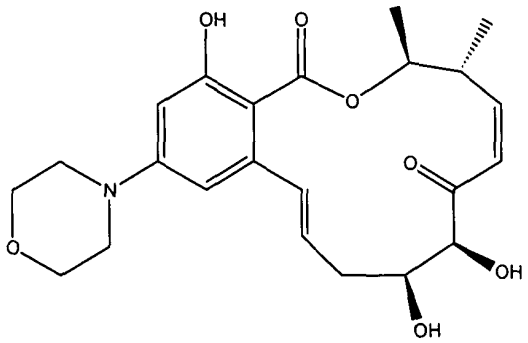
or pharmaceutically acceptable derivative thereof.

27. The composition of claim 1 wherein the compound has the structure:



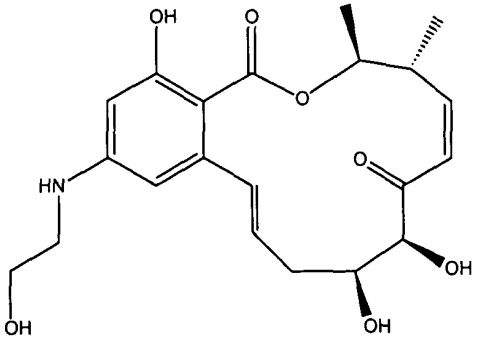
or pharmaceutically acceptable derivative thereof.

28. The composition of claim 1 wherein the compound has the structure:



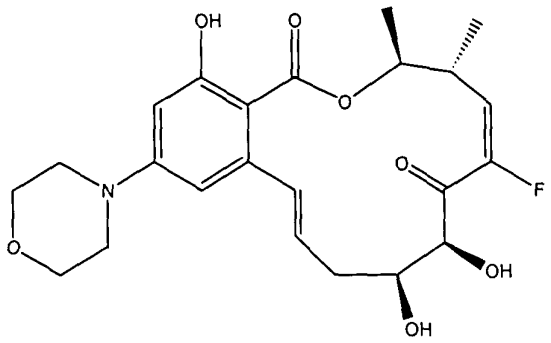
or pharmaceutically acceptable derivative thereof.

29. The composition of claim 1 wherein the compound has the structure:



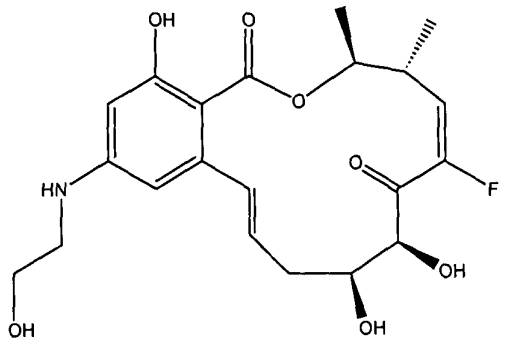
or pharmaceutically acceptable derivative thereof.

30. The composition of claim 1 wherein the compound has the structure:



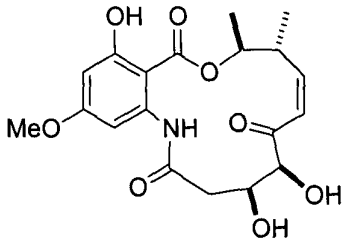
or pharmaceutically acceptable derivative thereof.

31. The composition of claim 1 wherein the compound has the structure:



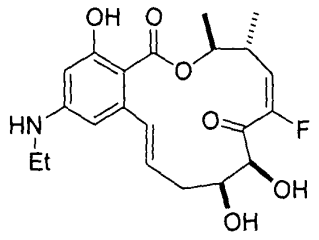
or pharmaceutically acceptable derivative thereof.

32. The composition of claim 1 wherein the compound has the structure:



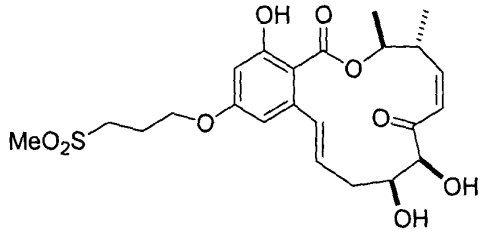
or pharmaceutically acceptable derivative thereof.

33. The composition of claim 1 wherein the compound has the structure:



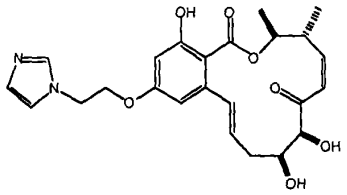
or pharmaceutically acceptable derivative thereof.

34. The composition of claim 1 wherein the compound has the structure:



or pharmaceutically acceptable derivative thereof.

35. The composition of claim 1 wherein the compound has the structure:



or pharmaceutically acceptable derivative thereof.

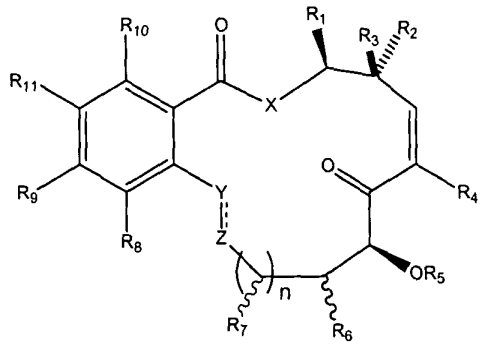
36. The pharmaceutical composition of claim 1, wherein the composition is for oral administration.

37. The pharmaceutical composition of claim 1, wherein the compound is present in an amount effective to inhibit production of a pro-inflammatory and/or immunologic cytokine.

38. The pharmaceutical composition of claim 37, wherein the pro-inflammatory and/or immunologic cytokine is TNFα, IL-1, IL-6, IL-8 or IL-2.

39. A method for treating an inflammatory and/or autoimmune disorder comprising:

systemically administering to a subject in need thereof a therapeutically effective amount of a compound having the structure:



(I)

or pharmaceutically acceptable derivative thereof;

wherein $\mathbf{R_1}$ is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl;

$\mathbf{R_2}$ and $\mathbf{R_3}$ are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or

R_1 and R_2, when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms; or

R_1 and R_3, when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms;

$\mathbf{R_4}$ is hydrogen or halogen;

$\mathbf{R_5}$ is hydrogen, an oxygen protecting group or a prodrug;

$\mathbf{R_6}$ is hydrogen, hydroxyl, or protected hydroxyl;

n is 0-2;

$\mathbf{R_7}$, for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

$\mathbf{R_8}$ is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or an aliphatic moiety optionally substituted with hydroxyl, protected hydroxyl, SR_{12}, or $NR_{12}R_{13}$;

R_9 is hydrogen, halogen, hydroxyl, protected hydroxyl, OR_{12}, SR_{12}, $NR_{12}R_{13}$, $-X_1(CH_2)_pX_2-R_{14}$, or is lower alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or $-X_1(CH_2)_pX_2-R_{14}$;

wherein R_{12} and R_{13} are, independently for each occurrence, hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or a protecting group, or R_{12} and R_{13}, taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of R_{12} and R_{13} are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein X_1 and X_2 are each independently absent, or are oxygen, NH, or -N(alkyl), or wherein X_2-R_{14} together are N_3 or are a saturated or unsaturated heterocyclic moiety,

p is 2-10, and

R_{14} is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is $-(C=O)NHR_{15}$ $-(C=O)OR_{15}$, or $-(C=O)R_{15}$, wherein each occurrence of R_{15} is independently hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or R_{14} is $-SO_2(R_{16})$, wherein R_{16} is an aliphatic moiety, wherein one or more of R_{14}, R_{15}, or R_{16} are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

R_8 and R_9 may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

R_{10} is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

R_{11} is hydrogen, hydroxyl or protected hydroxyl;

X is absent or is O, NH, N-alkyl, CH_2 or S;

Y is CHR_{17}, O, C=O, CR_{17} or NR_{17}; and **Z** is CHR_{18}, O, C=O, CR_{18} or NR_{18}, wherein each occurrence of R_{17} and R_{18} is independently hydrogen or aliphatic, or R_{17} and R_{18} taken

together is –O-, -CH_2- or -NR_{19}-, wherein R_{19} is hydrogen or lower alkyl, and Y and Z may be connected by a single or double bond; and

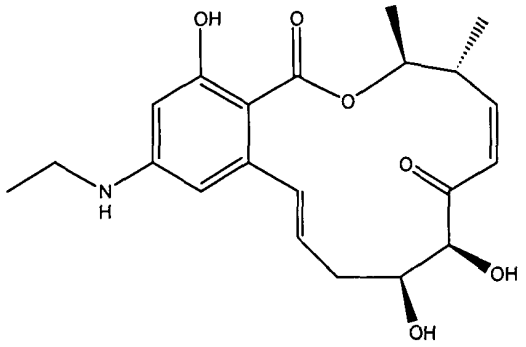
a pharmaceutically acceptable carrier or diluent.

40. The method of claim 39, wherein the compound is administered orally.

41. The method of claim 39 or 40, wherein the method is for treating a disorder selected from the group consisting of rheumatoid arthritis, psoriasis, asthma, cancer, sepsis, inflammatory bowel disease, atopic dermatitis, Crohn's disease, and autoimmune disorders.

42. The method of claim 41, wherein the method is for treating psoriasis.

43. The method of claim 41, wherein thecompound has the structure:



or pharmaceutically acceptable derivative thereof.

44. The method of claim 39, wherein the compound is present in an amount effective to inhibit production of a pro-inflammatory and/or immunologic cytokine.

45. The method of claim 44, wherein the pro-inflammatory and/or immunologic cytokine is TNFα, IL-1, IL-6, IL-8 or IL-2.